SYNLETT
Spotlight 430

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Dialkylaminodifluorosulfinium Salts: XtalFluor-E and XtalFluor-M

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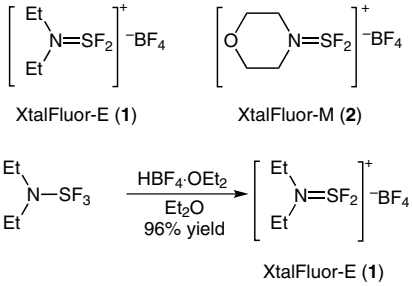
Introduction

Fluorination is an important reaction in medicinal chemistry.[1] Fluorinated analogues of biomolecules frequently show increased biological power, lipidic permeability and metabolic stability. Diethylaminosulfur trifluoride (DAST) has been widely used for directly replacing a hydroxyl group by fluorine under very mild conditions.[2,3] Nevertheless, the corrosive properties of DAST make it unsuitable for high-scale usage.

In this context, commercially available aminodifluorosulfinium salts,[4] such as XtalFluor-E (**1**) or XtalFluor-M (**2**), are efficient alternatives. These fluorinating agents are crystalline, more selective and significantly more stable[5] than Deoxo-Fluor or DAST and do not react violently with water.[6]

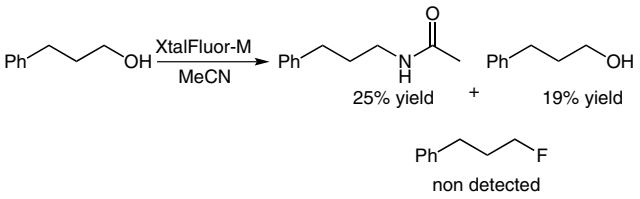
Reaction of DAST with tetrafluroboric acid provides, by elimination of HF, diethylaminodifluorosulfinium tetrafluoroborate **1** in excellent yield (Scheme 1).[5]



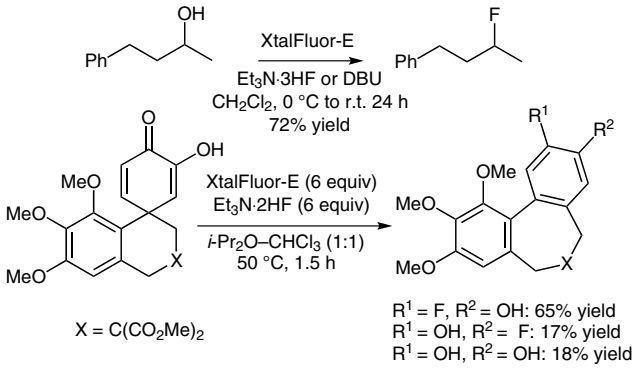
Scheme 1

Abstracts

(A) *Failure of Hydrocinnamyl Alcohol with XtalFluor-M:*
The reaction of hydrocinnamyl alcohol with **2** or **1** in acetonitrile provided an intractable mixture. For this reaction to proceed, the addition of exogenous sources of fluoride, such as $Et_3N{\cdot}3HF$ or $Et_3N{\cdot}2HF$, was necessary.[5]



(B) *Halogenation of Alcohols with XtalFluor Reagents:*
Reaction of primary, secondary and tertiary alcohols with **1** using $Et_3N{\cdot}3HF$ as a promoter gave the fluorinated nucleophilic substitution products. The addition order was a key parameter in this reaction. To obtain good selectivity and stereochemical integrity, 1,8-diazabicycloundec-7-ene (DBU) had to be used together with the fluorination agents.[5] A mixture of fluorinated bridged biphenyl systems has been obtained from 3-hydroxyspirodienones by means of a XtalFluor-E-promoted rearrangement. When compound **2** was used instead of compound **1**, substrate decomposition was observed.[6] Chlorination, bromination and iodination reaction of primary alcohols in good yield has been described using a combination of tetraethylammonium halide and XtalFluor-E.[7]



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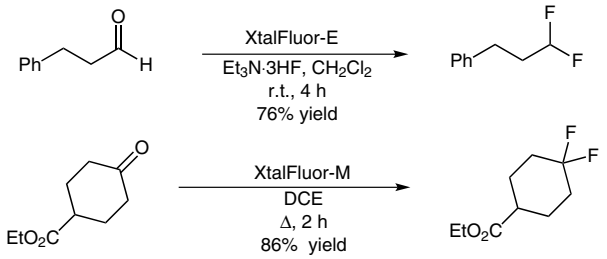
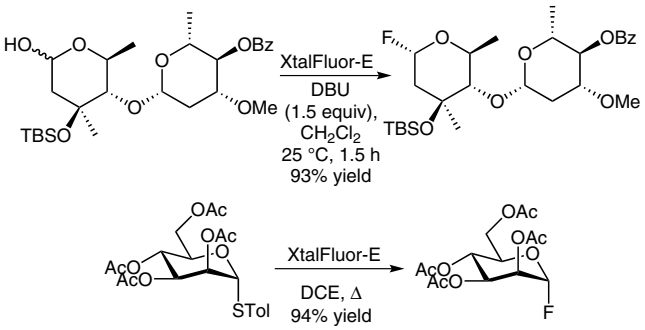
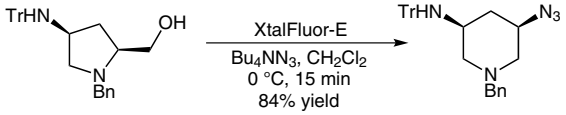
(C) *Geminal Difluorination of Carbonyl Groups:*
L´Heureux et al. have reported the geminal difluorination of carbonyl groups of aldehydes and ketones. They demonstrated that compound **1** alone was incapable of performing such transformations.[5,8] To obtain geminal difluorinated products, it was necessary to use a promoter and increase the temperature (e.g., CH_2Cl_2 or 1,2-dichloroethane at reflux).



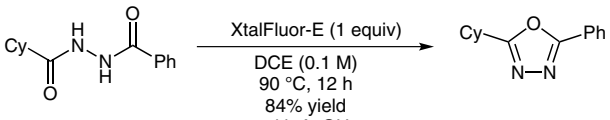
(D) *Fluorination Processes on Carbohydrate Derivatives:*
Fuchs and co-workers have recently reported the preparation of a fluorodisaccharide in excellent yield without side products using XtalFluor-E, thus eliminating the need for purification.[9] The effective preparation of glycosyl fluorides from thio-, seleno-, telluro- and glycosyl sulfoxides has been performed in 30 minutes by Williams and co-workers with evidence that fluoride is delivered by the tetrafluoroborate counterion [10]



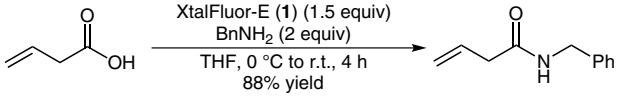
(E) *Enantioselective Ring Expansion of Prolinols:*
Direct ring expansion of *N*-alkyl prolinols to produce the corresponding 3-azidopiperidines in good and excellent regio-, diastereo- and enantioselectivity was achieved by using XtalFluor-E. Formation of an aziridinium intermediate which reacts with a nucleophile such as tetrabutylammonium azide (Bu_4NN_3) is proposed.[11]



(F) *Cyclodehydration Agents:*
Paquin and co-workers have recently reported[12] the use of **1** as a practical cyclodehydration agent to obtain 1,3,4-oxadiazoles among other nitrogen-containing heterocycles.[13] The addition of acetic acid improved the yield and selectivity of the oxadiazole formation.



(G) *Activating Agents for Carboxylic Acids:*
Compound **1** has proved to be an efficient coupling agent for the synthesis of amides by activation of the carboxylic acid.[14] Moreover, this reaction is carried out with primary and secondary amines in good yield without epimerization or racemization.



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